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(54) Title: SYNTHESIS OF SUBSTITUTED PYRAZOLOPYRIMIDINES

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(57) Abstract: Methods of making substituted pyrazolopyrimidines generally and, more particularly, N-methyl-N-(3-{3-[2-thienyl-  
carbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide. Such compounds have utility over a wide range of indications, includ-  
ing treatment of insomnia. In the practice of the present invention, improved techniques which do not require use and/or isolation  
of the pyrazole intermediate are disclosed, as well as improved techniques for making the reaction intermediates themselves. Such  
techniques offer significant advantages, including enhanced efficiency, particularly in the context of large scale manufacture.

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## SYNTHESIS OF SUBSTITUTED PYRAZOLOPYRIMIDINES

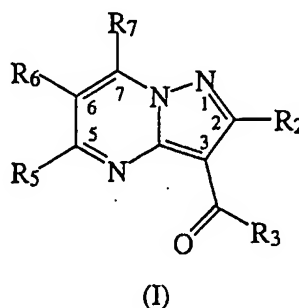
### TECHNICAL FIELD

5                    This invention is directed to the synthesis of substituted pyrazolopyrimidines, which compounds have utility over a wide range of indications including treatment of insomnia.

### BACKGROUND OF THE INVENTION

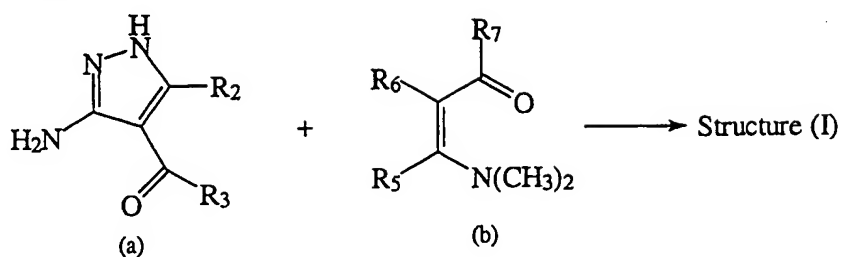
10                    U.S. Patent No. 4,521,422 to American Cyanamid Company is directed to certain aryl and heteroaryl[7-(aryl and heteroaryl)-pyrazolo[1,5-a]pyrimidin-3-yl]methanones which are active as anxiolytic, anticonvulsant, sedative-hypnotic and skeletal muscle relaxant agents. Such compounds may generally be classified as "substituted pyrazolopyrimidines" having the following structure (I):

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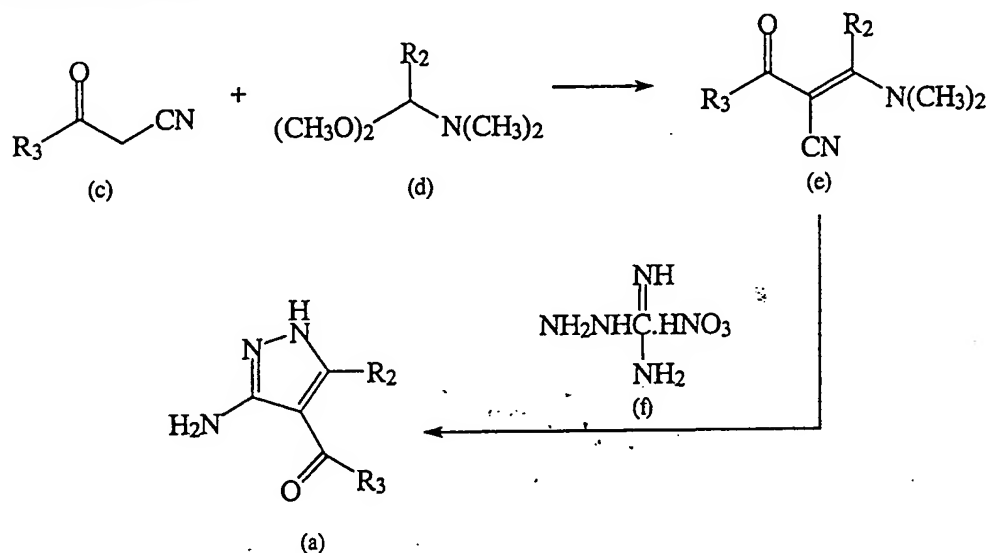


20                    wherein R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are as defined in U.S. Patent No. 4,521,422 (but under a different numbering scheme for the various R groups).

                    Compounds of structure (I) are made according to U.S. Patent No. 4,521,422 by reacting an appropriately substituted pyrazole (a) with an appropriately substituted 3-dimethylamino-2-propen-1-one (b) as represented by the following Reaction Scheme A:

Reaction Scheme A

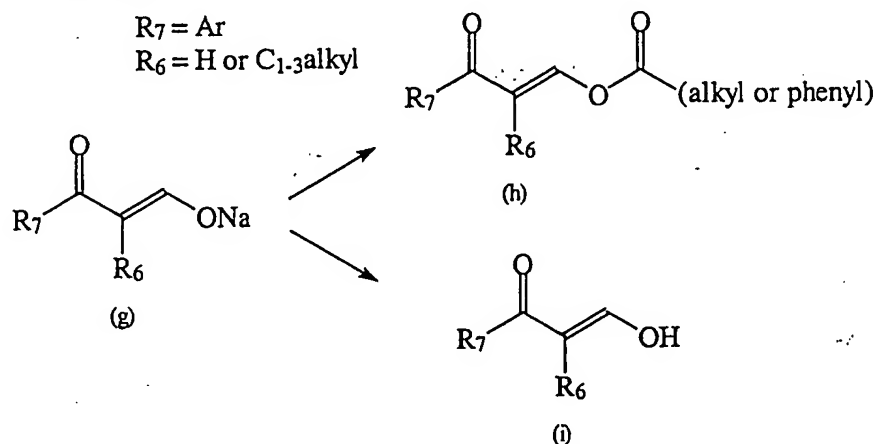
5 U.S. Patent No. 4,900,836, also to American Cyanamid Company, discloses novel pyrazoles (a) for use in Reaction Scheme A. More specifically, in this patent pyrazoles (a) are made, as represented below in Reaction Scheme B, by reacting appropriately substituted acetonitrile (c) with a dimethylamide dimethyl acetal (d) to yield the corresponding propanenitrile (e), which is then reacted with  
 10 aminoguanidine nitrile (f) to give the correspondingly substituted pyrazole (a).

Reaction Scheme B

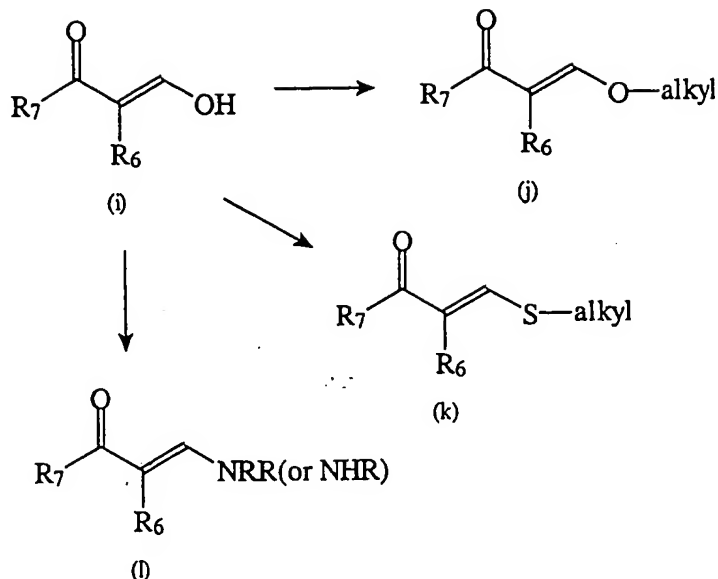
15 U.S. Patent No. 4,521,422 also discloses the synthesis of substituted pyrazolopyrimidines of structure (I) using starting intermediates other than substituted 3-dimethylamino-2-propen-1-ones (b). For example, as represented by Reaction

Scheme C, U.S. Patent No. 4,521,422 teaches that the intermediate alkali metal salts of hydroxymethyleneketones (g) can be acylated by reacting with acid chlorides or anhydrides to give O-acyl derivatives (h), and that neutralization of (g) with certain acids affords hydroxymethylene ketones (i), all of which may be reacted with  
5 pyrazole (a) to give compounds of structure (I).

Reaction Scheme C



10 Further, U.S. Patent No. 4,521,422 discloses that hydroxymethyleneketones (i) may be converted to other aldehyde equivalents, such as alkoxymethyleneketones (j), alkylthiomethyleneketones (k) and aminomethyleneketones (l) - as represented by Reaction Scheme D - and reacted with  
15 pyrazole (a) to give compounds of structure (I). Other hydroxymethyleneketone and derivatives which are chemical equivalents of the same may also be used, such as 2-(dialkylamino)-1-aryl or (heteroaryl)-2-propen-1-ones.

Reaction Scheme D

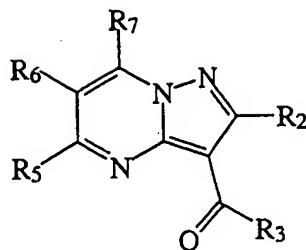
In addition, other United States patents have issued directed to the  
 5 synthesis of substituted pyrazolopyrimidines. For example, U.S. Patent Nos.  
 4,654,347 and 4,626,538, both to American Cyanamide, disclose substituted  
 pyrazolopyrimidines of structure (I) made by the techniques discussed above, but  
 having different substituents than those of U.S. Patent No. 4,521,422.

While U.S. Patent Nos. 4,521,422 and 4,900,836, among others, teach  
 10 techniques for the synthesis of compounds of structure (I), such procedures are  
 relatively time consuming, involve numerous steps, and are not particularly  
 economical or efficient for large-scale synthesis. Accordingly, there is a need in the  
 art for improved synthetic techniques which overcome these shortcomings. The  
 present invention fulfills these needs, and provides further related advantages.

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SUMMARY OF THE INVENTION

In brief, the present invention is directed to the synthesis of substituted  
 pyrazolopyrimidines having the following structure (I), which compounds have utility  
 over a wide range of indications, including treatment of insomnia.



(I)

In structure (I) above, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> may be any of a number of  
5 substituents, and represent the remainder of the compound. Thus, in one  
embodiment, the present invention is directed generally to the synthesis of the  
pyrazolopyrimidine "core" or "template" itself, regardless of the nature of the various  
R substituents.

In a more specific embodiment, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> of structure (I)  
10 are as defined in U.S. Patent No. 4,521,422, but under a different numbering scheme  
for the respective R groups. In particular, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> of structure (I)  
correspond to R<sub>2</sub>, R<sub>1</sub>, R<sub>5</sub>, R<sub>4</sub> and R<sub>3</sub>, respectively, of U.S. Patent No. 4,521,422.

In another more specific embodiment, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> of  
structure (I) are as defined in U.S. Patent No. 4,654,347, wherein R<sub>5</sub> and R<sub>6</sub> of  
15 structure (I) are both hydrogen and R<sub>2</sub>, R<sub>3</sub> and R<sub>7</sub> of structure (I) correspond to R<sub>2</sub>, R<sub>1</sub>  
and R<sub>3</sub>, respectively, of U.S. Patent No. 4,654,347.

In yet another more specific embodiment, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> of  
structure (I) are as defined in U.S. Patent No. 4,626,538, wherein R<sub>5</sub> and R<sub>6</sub> of  
structure (I) are both hydrogen and R<sub>2</sub>, R<sub>3</sub> and R<sub>7</sub> of structure (I) correspond to R<sub>2</sub>, R<sub>4</sub>  
20 (when R<sub>1</sub> is -C(=O)R<sub>4</sub>) and R<sub>3</sub>, respectively, of U.S. Patent No. 4,626,538.

For purpose of convenience, the more specific embodiments disclosed  
above are also referred to herein as "the R groups of U.S. Patent Nos. 4,521,422,  
4,654,347 and 4,626,538." Thus, in one embodiment, the present invention is  
directed to the synthesis of substituted pyrazolopyrimidines having structure (I)  
25 above, which compounds have utility over a wide range of indications, including  
treatment of insomnia, wherein structure (I) is substituted with the R groups of U.S.  
Patent Nos. 4,521,422, 4,654,347 and 4,626,538.

The synthetic techniques of this invention represent significant improvements over the prior techniques, including those disclosed in U.S. Patent Nos. 4,521,422 and 4,900,836, particularly with regard to enhanced efficiency for large scale manufacture, reduced cost, better yield and/or simplified reaction conditions. In addition, improved techniques are also disclosed which do not require isolation of the pyrazole intermediate, as well as improved techniques for making intermediates for synthesis of compounds of structure (I).

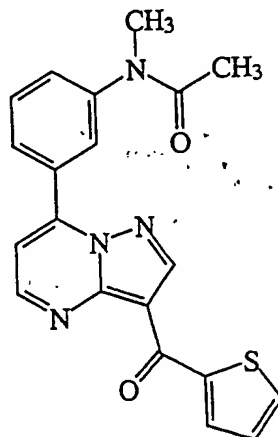
These and other aspects of this invention will be apparent upon reference to the following detailed description.

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## DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is directed to improved synthetic routes for the synthesis of substituted pyrazolopyrimidines which are active as anxiolytic, anticonvulsant, sedative-hypnotic and skeletal muscle relaxant agents. Such compounds are represented by structure (I) above, and have previously been disclosed in U.S. Patent Nos. 4,521,422, 4,900,836, 4,654,347 and 4,626,538 (which patents are each incorporated herein by reference in their entirety).

More specifically, in one embodiment of this invention, the pyrazolopyrimidine of structure (I) is N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-  
[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide, which compound has the following structure (hereinafter referred to as "Compound 1" or "1"):



Compound 1

In Reaction Scheme 5, N-alkylation of m-acetamidoacetophenone 2 using conditions of sodium hydride and methyl iodide (or, alternatively, dimethylsulfate) provides acetophenone 3. A mixture of both acetophenone 3 and nitrile 4 are diluted with toluene. An excess of dimethylformamidedimethylacetal (DMFDMA) is added and the mixture refluxed until the starting materials are consumed. A workup involving the removal of toluene and excess DMFDMA is employed to complete this stage of the synthesis. Without isolation of the enaminone intermediates, ethanol is added followed by an appropriate amount of aminoguanidinium nitrate and sodium hydroxide as shown in Reaction Scheme 5.

10 The mixture is heated until consumption of the thiophene intermediate is complete. The crude material is heated in acetic acid and the product is isolated and purified. The benefits of this technique are several, particularly in the context of not having to isolate reaction intermediates, such as the pyrazole intermediate.

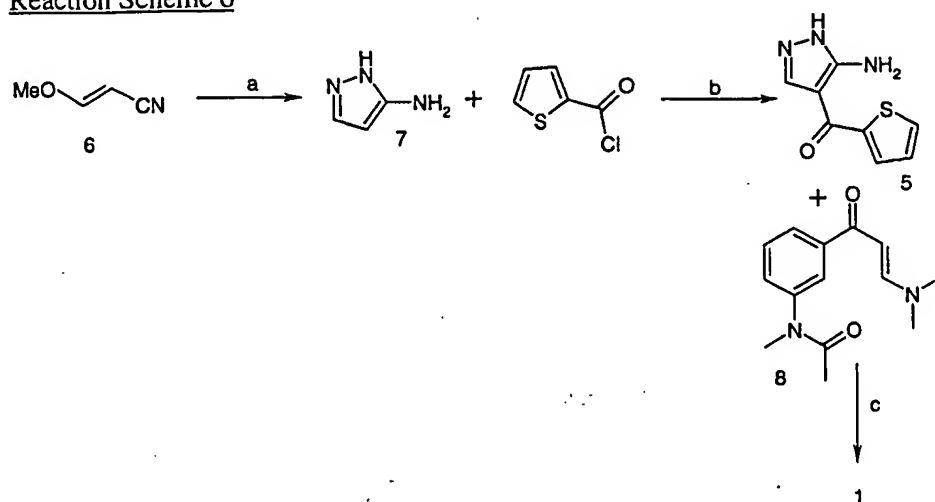
Accordingly, in this embodiment, a method is disclosed for making

15 Compound 1, in a single reaction mixture, by the following steps:

- (a) alkylating m-acetamidoacetophenone 2 to provide acetophenone 3;
- (b) reacting nitrile 4 with acetophenone 3 in the presence of DMFDMA and a solvent until nitrile 4 and acetophenone 3 are consumed;
- 20 (c) removing any excess DMFDMA and solvent and, without isolation of the intermediate reaction products from step (b), converting the reaction products upon reaction with aminoguanidine to compound 1; and
- (d) isolating Compound 1.

25 In another embodiment, a compound of structure (I) generally, or Compound 1 specifically, is prepared utilizing an improved technique for the synthesis of the pyrazole intermediate, as depicted in the following Reaction Scheme 6.



Reaction Scheme 6

Reagents: (a)  $\text{NH}_2\text{NH}_2\text{H}_2\text{O}$ ; (b) heat; (c)  $\text{HOAc}$ , reflux

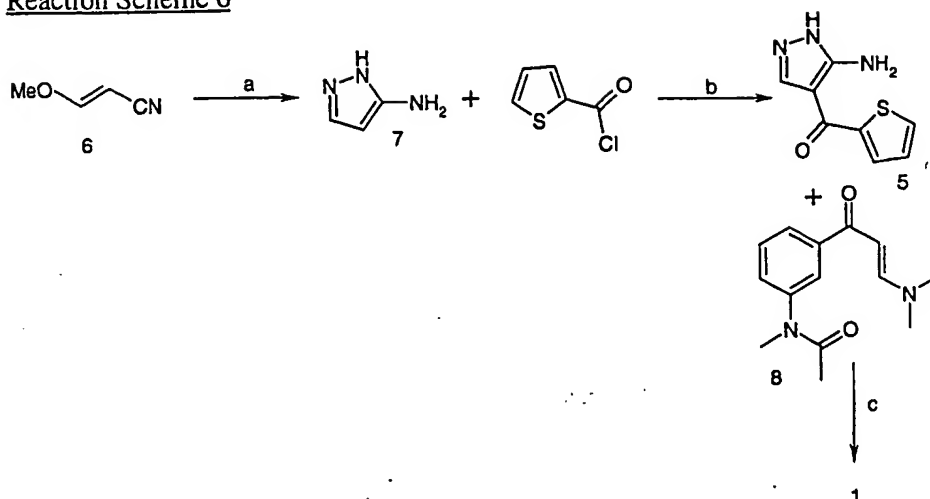
- 5 In Reaction Scheme 6, pyrazole 5 is prepared by the treatment of methoxyacrylonitrile 6 with hydrazine to afford the 3-aminopyrazole 7. Addition of 2-thiophenecarboxylic acid chloride to a solution of aminopyrazole 7 initially provides an amide intermediate, which upon heating leads to an intramolecular rearrangement affording pyrazole 5. This is then cyclized with the known enaminone
- 10 8 under the standard conditions providing the desired product, Compound 1.

Accordingly, in the practice of this embodiment, a method is disclosed for making Compound 1 by the following steps:

- (a) treating methoxyacrylonitrile 6 with hydrazine to afford 3-aminopyrazole 7;
- 15 (b) reacting 3-aminopyrazole 7 with 2-thiophenecarboxylic acid chloride to yield pyrazole 5; and
- (c) cyclizing pyrazole 5 with enaminone 8 to yield Compound 1.

In yet another embodiment, a compound of structure (I) generally, or

20 compound 1 specifically, is prepared by cyclizing the pyrazole intermediate as depicted in the following Reaction Scheme 7.

Reaction Scheme 6

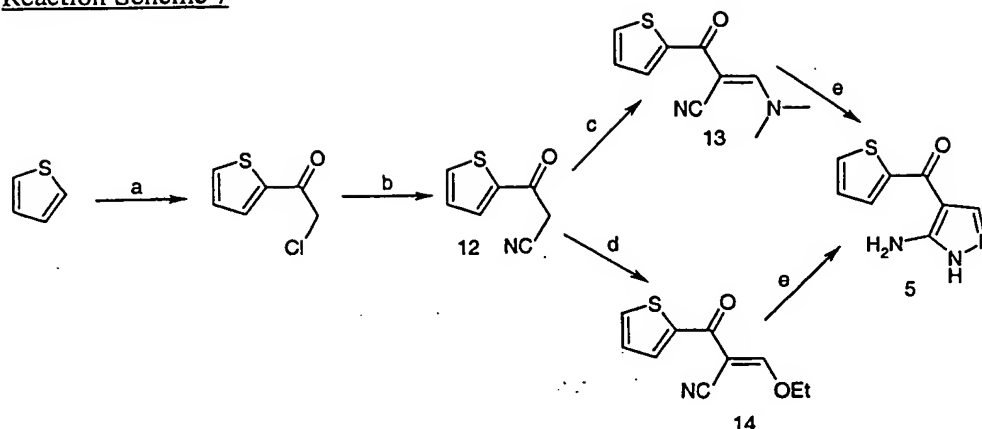
Reagents: (a)  $\text{NH}_2\text{NH}_2\text{H}_2\text{O}$ ; (b) heat; (c)  $\text{HOAc}$ , reflux

5 In Reaction Scheme 6, pyrazole 5 is prepared by the treatment of methoxyacrylonitrile 6 with hydrazine to afford the 3-aminopyrazole 7. Addition of 2-thiophenecarboxylic acid chloride to a solution of aminopyrazole 7 initially provides an amide intermediate, which upon heating leads to an intramolecular rearrangement affording pyrazole 5. This is then cyclized with the known enaminone 8 under the standard conditions providing the desired product, Compound 1.

Accordingly, in the practice of this embodiment, a method is disclosed for making Compound 1 by the following steps:

- (a) treating methoxyacrylonitrile 6 with hydrazine to afford 3-aminopyrazole 7;
- 15 (b) reacting 3-aminopyrazole 7 with 2-thiophenecarboxylic acid chloride to yield pyrazole 5; and
- (c) cyclizing pyrazole 5 with enaminone 8 to yield Compound 1.

20 In yet another embodiment, a compound of structure (I) generally, or compound 1 specifically, is prepared by cyclizing the pyrazole intermediate as depicted in the following Reaction Scheme 7.

Reaction Scheme 7

Reagents: (a)  $\text{AlCl}_3$ ; (b)  $\text{KCN}$ ,  $\text{EtOH}$ ; (c) DMFDMA; (d)  $\text{HC}(\text{OEt})_3$ ; (e) aminoguanidine.

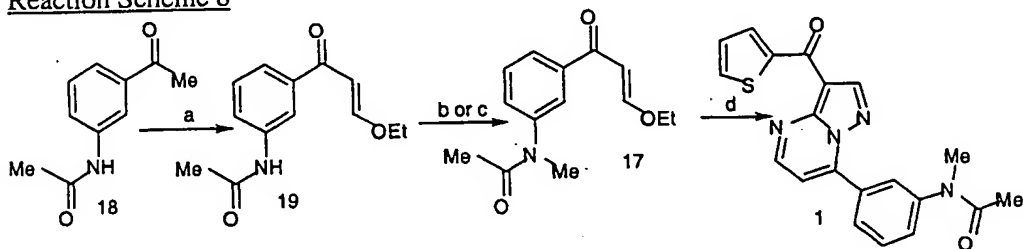
- 5 In Reaction Scheme 7, thiophene is acylated under Friedel-Crafts conditions with chloroacetylchloride yielding the corresponding acylthiophene. Nucleophilic displacement of the chloride with potassium cyanide affords nitrile 12. This is converted to enaminone 13 with DMFDMA or the ethoxyenolether 14 using triethyl orthoformate. Pyrazole intermediate 5 is prepared from either 13 or 14 using
- 10 standard conditions involving aminoguanidine or hydrazine.

Accordingly, in the practice of this embodiment, a method is disclosed for making Compound 1 by the following steps:

- (a) converting nitrile 12 (which may be obtained by reacting thiophene with chloroacetylchloride to yield 2-thiophenecarboxylic acid chloride, and
- 15 converting the same to nitrile 12 by displacement of the chloride with cyanide) to (i) enaminone 13 with DMFDMA, or to (ii) ethoxyenolether 14 with triethyl orthoformate; and
- (c) preparing pyrazole 5 from either enaminone 13 or ethoxyenolether 14; and
- 20 (d) cyclizing pyrazole 5 with enaminone 8 to yield Compound 1.

In still a further embodiment, a compound of structure (I) generally, or Compound 1 specifically, is prepared by cyclizing pyrazole intermediate 5 as depicted in the following Reaction Scheme 8.

# 5 Reaction Scheme 8



Reagents: (a)  $\text{HC}(\text{OEt})_3$ ; (b)  $\text{MeI}$ ,  $\text{NaH}$ ; (c)  $\text{Me}_2\text{SO}_4$ ; (d) 5,  $\text{AcOH}$ , reflux

In Reaction Scheme 8, enol ether 17 is employed in a cyclization reaction. Treatment of the acetophenone 18 with triethyl orthoformate, followed by heating, affords the enol ether 19. This is N alkylated with iodomethane or dimethyl sulfate yielding enol ether 17. Cyclization of 17 with pyrazole intermediate 5 in acetic acid leads to the desired product, Compound 1.

Accordingly, in the practice of this embodiment, a method is disclosed for making Compound 1 by the following steps:

- (a) treatment of acetophenone 18 with triethyl orthoformate to yield enol ether 19;
- (b) alkylating enol ether 19 to afford enol ether 17; and
- (c) cyclizing enol ether 17 with pyrazole 5 to yield Compound 1.

20

In a preferred embodiment, one or more of the alkylation steps of this invention, particularly the alkylation involved in the formation of enaminone 8 employed in Reaction Schemes 1, 2 and 3 above, occur under phase transfer conditions. As used herein, "phase transfer conditions" means an organic substrate is dissolved in an organic solvent and the nucleophilic reagent is dissolved in an aqueous phase, a phase transfer catalyst is used to carry the nucleophile from the

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aqueous phase into the organic phase to react with the substrate. More specifically, phase transfer conditions in the context of this invention may be obtained by utilizing, for example, a phase transfer catalyst (such as quaternary ammonium or phosphonium salts, crown ethers and polyethylene glycol ethers) in a polar organic solvent (such as methylene chloride, benzotrifluoride, or toluene) with an aqueous phase containing a base (such as sodium or potassium hydroxide).

Although the above Reaction Schemes 1 through 8 depict the synthesis of Compound 1 specifically, it should be understood that these schemes apply generally to compounds of structure (I) by appropriate selection of the various R groups thereof. Thus, in each of the above Reaction Schemes 1 through 8, the specific R groups associated with the synthesis of Compound 1 may be replaced with the corresponding R groups of U.S. Patent Nos. 4,521,422, 4,654,347 and 4,626,538 to synthesize the full scope of compounds encompassed within structure (I). Similarly, for each of the intermediates employed in Reaction Schemes 1 through 8, it should be understood that each of these intermediates, while specifically depicted in the context of Compound 1 synthesis, encompass intermediates substituted by the corresponding R groups of U.S. Patent Nos. 4,521,422, 4,654,347 and 4,626,538.

While the R groups of U.S. Patent Nos. 4,521,422, 4,654,347 and 4,626,538 are fully disclosed in each of these respective patents, for purpose of completeness they are repeated below (using the number scheme for each of the various R groups as disclosed in those patents):

U.S. Patent No. 4,521,422:

R<sub>1</sub> is selected from the group consisting of unsubstituted phenyl; phenyl mono- or di-substituted by halogen, alkoxy(C<sub>1</sub>-C<sub>3</sub>) or alkyl(C<sub>1</sub>-C<sub>3</sub>); phenyl mono-substituted by trifluoromethyl, alkylthio(C<sub>1</sub>-C<sub>3</sub>), alkylamino(C<sub>1</sub>-C<sub>3</sub>), dialkylamino(C<sub>1</sub>-C<sub>3</sub>), methylenedioxy, alkylsulfonyl(C<sub>1</sub>-C<sub>3</sub>) or alkanoylamino(C<sub>1</sub>-C<sub>3</sub>); naphthalenyl; thiazolyl; biphenyl; thienyl; furanyl; pyridinyl; substituted thiazolyl; substituted biphenyl; substituted thienyl; and substituted pyridinyl wherein the

substituents are selected from one or two of the group consisting of halogen, alkoxy(C<sub>1</sub>-C<sub>3</sub>) and alkyl(C<sub>1</sub>-C<sub>3</sub>);

R<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> are each selected from the group consisting of hydrogen and alkyl(C<sub>1</sub>-C<sub>3</sub>); and

5 R<sub>3</sub> is selected from the group consisting of unsubstituted phenyl, phenyl mono-substituted by halogen, trifluoromethyl, alkoxy(C<sub>1</sub>-C<sub>3</sub>), amino, alkyl(C<sub>1</sub>-C<sub>3</sub>), alkylamino(C<sub>1</sub>-C<sub>6</sub>), dialkylamino(C<sub>1</sub>-C<sub>3</sub>), alkanoylamino(C<sub>1</sub>-C<sub>6</sub>), N-alkyl(C<sub>1</sub>-C<sub>6</sub>)alkanoylamino(C<sub>1</sub>-C<sub>6</sub>), cyano or alkylthio(C<sub>1</sub>-C<sub>3</sub>); furanyl; thienyl; pyridinyl; and pyridine-1-oxide.

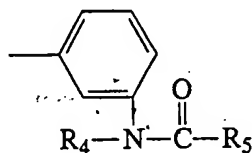
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U.S. Patent No. 4,654,347:

R<sub>1</sub> is selected from the group consisting of unsubstituted phenyl; phenyl mono- or disubstituted by halogen, alkyl(C<sub>1</sub>-C<sub>3</sub>) or alkoxy(C<sub>1</sub>-C<sub>3</sub>); phenyl monosubstituted by trifluoromethyl, alkylthio(C<sub>1</sub>-C<sub>3</sub>), alkylamino(C<sub>1</sub>-C<sub>3</sub>),  
15 dialkylamino(C<sub>1</sub>-C<sub>3</sub>), methylenedioxy, alkylsulfonyl(C<sub>1</sub>-C<sub>3</sub>) or alkanoylamino(C<sub>1</sub>-C<sub>3</sub>); naphthalenyl; thiazolyl; biphenyl; thienyl; furanyl; pyridinyl; substituted thiazolyl; substituted biphenyl; substituted thienyl; and substituted pyridinyl, wherein the substituents are selected from one or two of the groups consisting of halogen, alkyl(C<sub>1</sub>-C<sub>3</sub>) and alkoxy(C<sub>1</sub>-C<sub>3</sub>);

20 R<sub>2</sub> is selected from the group consisting of hydrogen and alkyl(C<sub>1</sub>-C<sub>3</sub>);

R<sub>3</sub> is



R<sub>4</sub> is selected from the group consisting of hydrogen, alkenyl(C<sub>2</sub>-C<sub>6</sub>), —CH<sub>2</sub>C≡CH, cycloalkyl(C<sub>3</sub>-C<sub>6</sub>)methyl, —CH<sub>2</sub>OCH<sub>3</sub> and —CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>; and

25 R<sub>5</sub> is selected from the group consisting of hydrogen, cycloalkyl(C<sub>3</sub>-C<sub>6</sub>), —O-alkyl(C<sub>1</sub>-C<sub>6</sub>), —NH-alkyl(C<sub>1</sub>-C<sub>3</sub>), —N-dialkyl(C<sub>1</sub>-C<sub>3</sub>),

$-(CH_2)_n-O-alkyl(C_1-C_3),$   $-(CH_2)_n-NH-alkyl(C_1-C_3),$   
 $-(CH_2)_n-N-dialkyl(C_1-C_3),$  where  $n$  is an integer 1 to 3 inclusive, and  $R_5$  may be  
 $alkyl(C_1-C_6),$  when  $R_4$  is not hydrogen.

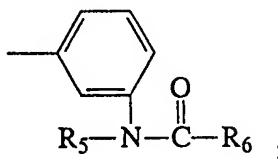
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U.S. Patent No. 4,626,538:

$R_1$  is  $-C(=O)R_4;$

$R_2$  is selected from the group consisting of hydrogen and  $alkyl(C_1-C_3);$

$R_3$  is



10

$R_4$  is selected from the group consisting of hydrogen,  $alkyl(C_1-C_6)$  and  $alkoxy(C_1-C_6);$

$R_5$  is selected from the group consisting of hydrogen,  $alkyl(C_1-C_6),$   $alkenyl(C_2-C_6),$   $-CH_2C\equiv CH,$   $cycloalkyl(C_3-C_6)methyl,$   $-CH_2OCH_3$  and  $-CH_2CH_2OCH_3;$  and

15

$R_6$  is selected from the group consisting of  $alkyl(C_1-C_6),$   $cycloalkyl(C_3-C_6),$   $-O-alkyl(C_1-C_6),$   $-NH-alkyl(C_1-C_3),$   $-N-dialkyl(C_1-C_3),$   $-(CH_2)_n-O-alkyl(C_1-C_3),$   $-(CH_2)_n-NH-alkyl(C_1-C_3)$  and  $-(CH_2)_n-N-dialkyl(C_1-C_3),$  where  $n$  is an integer 1 to 3 inclusive.

20

In addition to the above synthetic embodiments, the present invention is also directed to substituted pyrazolopyrimidines of structure (I), particularly Compound 1, made according to any one (or more) of the methods of this invention, as well as to novel intermediates therefor, including each of the intermediates set forth in Reaction Schemes 1 through 8 above with appropriate substitution by the

25

corresponding R groups of U.S. Patent Nos. 4,521,422, 4,654,347 and 4,626,538.

The substituted pyrazolopyrimidines of this invention have utility as anxiolytic, anticonvulsant, sedative-hypnotic and skeletal muscle relaxant agents. More specifically, these compounds have particular utility in the context of treating insomnia by inducing sedation or hypnosis, as well as skeletal muscle relaxation.

5 Typically, such compounds are administered in the form of a pharmaceutical composition, in dosage unit form, in an amount which is effective to treat the condition of interest comprising. Generally, this is from about 1-750 mg of compound in combination with an appropriate pharmaceutically acceptable carrier. In a typical embodiment, the compound is present in the pharmaceutical composition

10 in an amount ranging from 2 mg to 60 mg per dosage depending upon the route of administration. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carriers are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers include

15 saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a compound of structure (I), diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the compound in an appropriate manner,

20 and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

As noted above, the compounds of this invention have utility in the context of treating conditions which benefit from administration of agents which possess anxiolytic, anti-anoxic, sleep-inducing, hypnotic, anticonvulsant, and/or

25 skeletal muscle relaxant properties. Such conditions include insomnia specifically, as well as sleep disorders generally and other neurological and psychiatric complaints, anxiety states, vigilance disorders, such as for combating behavioral disorders attributable to cerebral vascular damage and to the cerebral sclerosis encountered in geriatrics, epileptic vertigo attributable to cranial trauma, and for metabolic

30 encephalopathies.

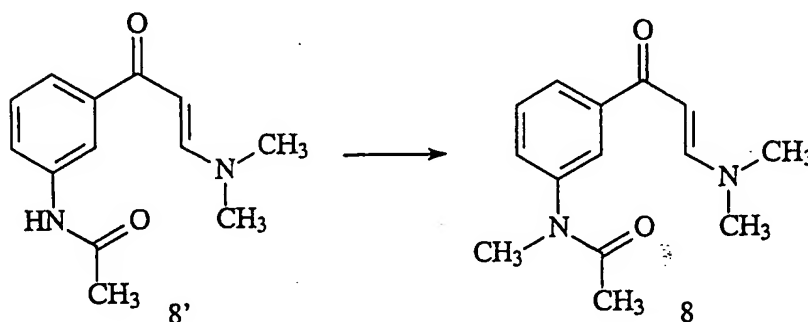


Representative routes of administration to a patient in need thereof include systemic administration, preferably in the form of a pharmaceutical composition as noted above. As used herein, systemic administration encompasses both oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parenteral administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

The following example is offered by way of illustration, not limitation.

#### EXAMPLE

FORMATION OF ENAMINONE 8 OF REACTION SCHEMES 1, 2 AND/OR 3  
UNDER PHASE TRANSFER CONDITIONS



To enaminone 8' (25 g, 107.6 mmol) in benzotrifluoride (92 mL) and dichloromethane (160 mL) was added tetrabutylammonium sulfate (2 g, 5.9 mmol). To the mixture was added of dimethyl sulfate (16 g, 126.7 mmol). To the mixture was added 200 g of 50% aqueous sodium hydroxide solution and the mixture vigorously stirred for 6 hours, keeping the reaction temperature less than 40°C. Upon consumption of starting material, 200 mL of water was carefully added keeping the

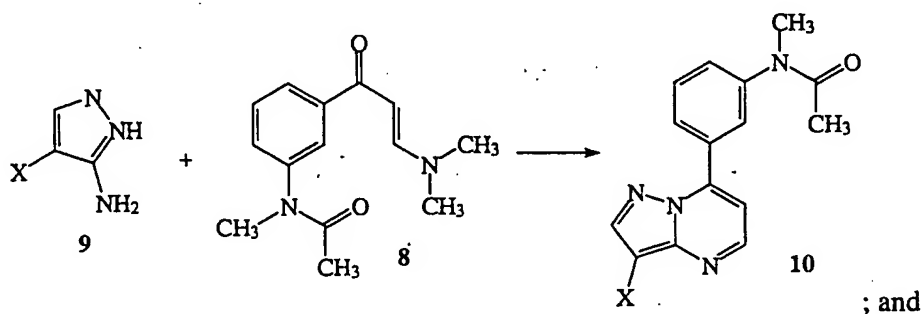
reaction temperature less than 40°C. The aqueous phase was separated and the organic phase was washed three times with water and dried over magnesium sulfate. The dichloromethane was removed *in vacuo* affording a yellow solid. The solid was filtered, washed with benzotrifluoride and dried *in vacuo* affording alkylated  
5 enaminone 8 (19 g, 72% yield).

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the  
10 invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

1. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

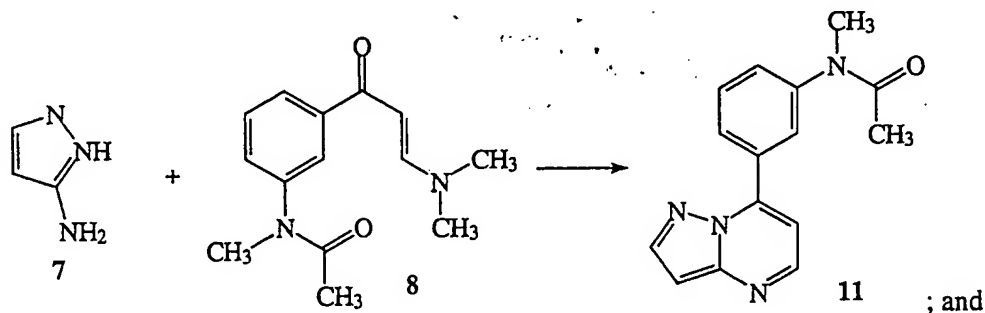
(a) reacting pyrazole 9 with enaminone 8 to yield the corresponding halopyrazolopyrimidine 10



(b) reacting halopyrazolopyrimidine 10 with either (1) 2-thiophenecarboxylic acid chloride in the presence of zinc or magnesium, or (2) 2-thiophene boronic acid in the presence of carbon monoxide and a palladium catalyst, to yield Compound 1.

2. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

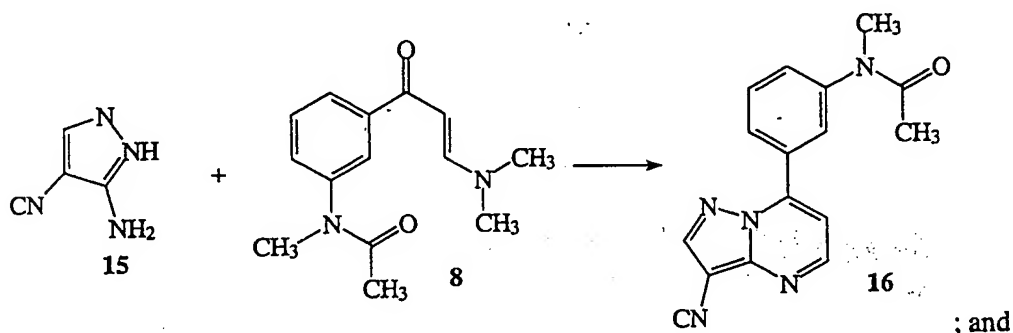
(a) cyclizing aminopyrazole 7 with enaminone 8 to yield pyrazolopyrimidine 11



(b) reacting pyrazolopyrimidine 11 with 2-thiophenecarboxylic acid chloride in the presence of a Lewis acid to yield Compound 1.

3. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

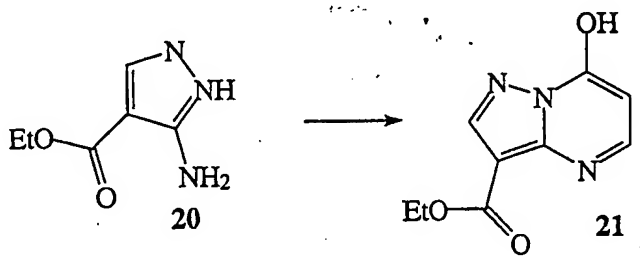
(a) cyclizing cyanoaminopyrazole 15 with enaminone 8 to yield nitrile-pyrazolopyrimidine 16



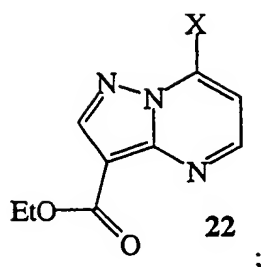
(b) reacting nitrile-pyrazolopyrimidine 16 with (1) a Grignard reagent prepared from magnesium and 2-bromothiophene, or (2) with 2-lithium thiophene followed by hydrolysis, to give compound 1.

4. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

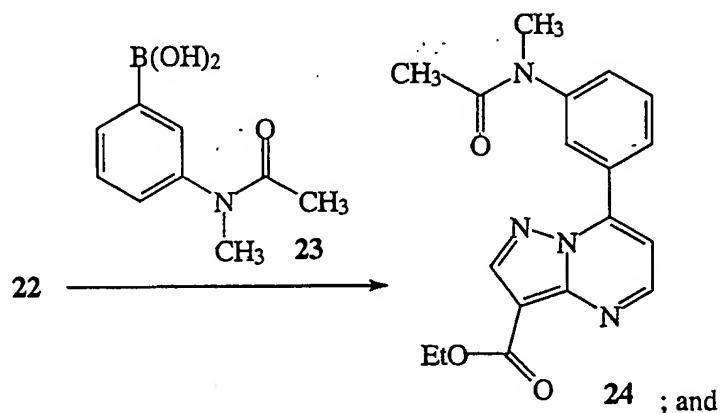
(a) condensing aminopyrazole 20 with (1) formyl propionic acid methyl ester, or (2) ethyl 3,3-diethoxypropionate, to yield pyrazolopyrimidone 21



(b) converting pyrazolopyrimidone 21 to halopyrazolopyrimidine 22



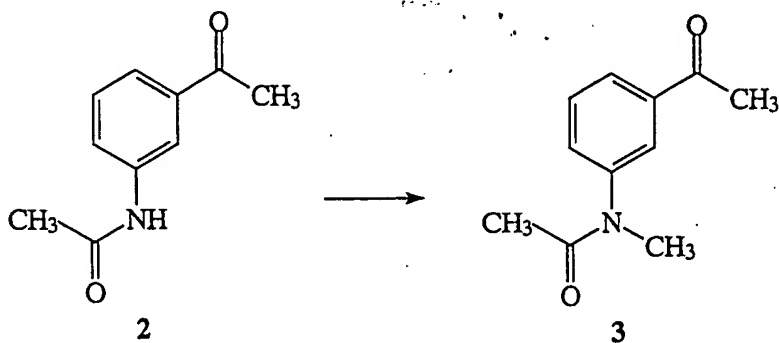
(c) coupling halopyrazolopyrimidine 22 with boronic acid 23 to yield pyrazolopyrimidine 24



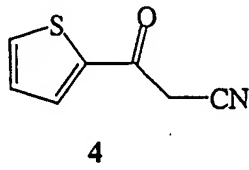
(d) reacting pyrazolopyrimidine 24 with (1) a Grignard reagent prepared from magnesium and 2-bromothiophene, or (2) with 2-lithium thiophene followed by hydrolysis, to give Compound 1.

5. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

(a) alkylating m-acetamidoacetophenone 2 to provide acetophenone 3



(b) reacting nitrile 4 with acetophenone 3 in the presence of DMFDMA and a solvent until nitrile 4 and acetophenone 3 are consumed

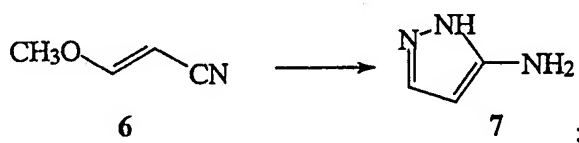


(c) removing any excess DMFDMA and solvent and, without isolation of the intermediate reaction products from step (b), converting the reaction products upon reaction with aminoguanidine to Compound 1; and

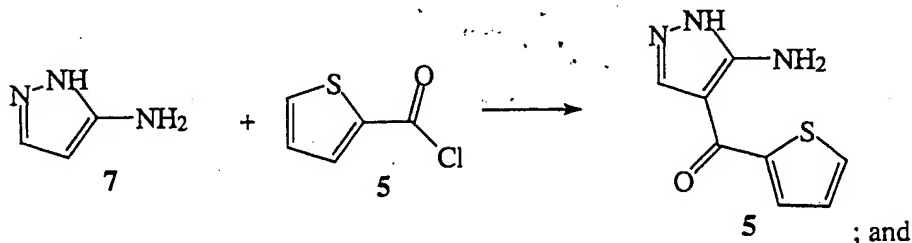
(d) isolating Compound 1.

6. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

(a) treating methoxyacrylonitrile 6 with hydrazine to afford 3-aminopyrazole 7;

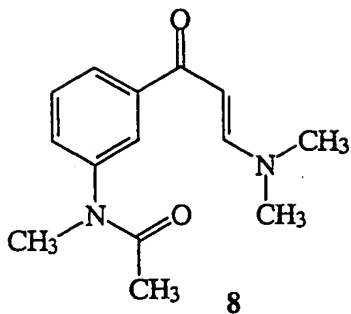


(b) reacting 3-aminopyrazole 7 with 2-thiophenecarboxylic acid chloride to yield pyrazole 5



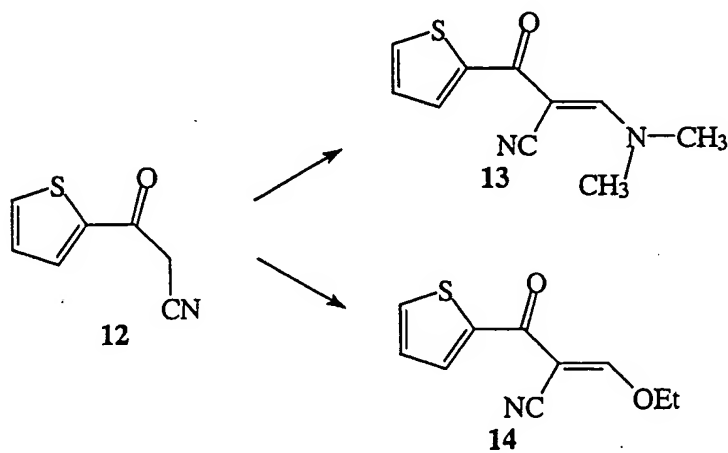
(c) cyclizing pyrazole 5 with enaminone 8 to yield Compound 1

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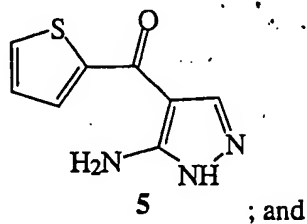


7. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-1,5- $\alpha$ -pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

(a) converting nitrile 12 to (i) enaminone 13 with DMFDMA, or to (ii) ethoxyenolether 14 with triethyl orthoformate

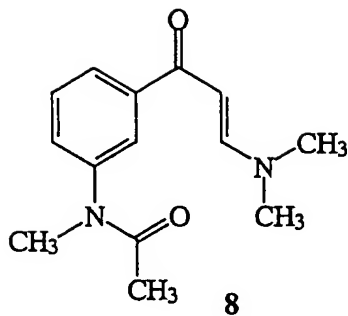


(b) preparing pyrazole 5 from either enaminone 13 or ethoxyenolether 14



(c) cyclizing pyrazole 5 with enaminone 8 to yield compound 1

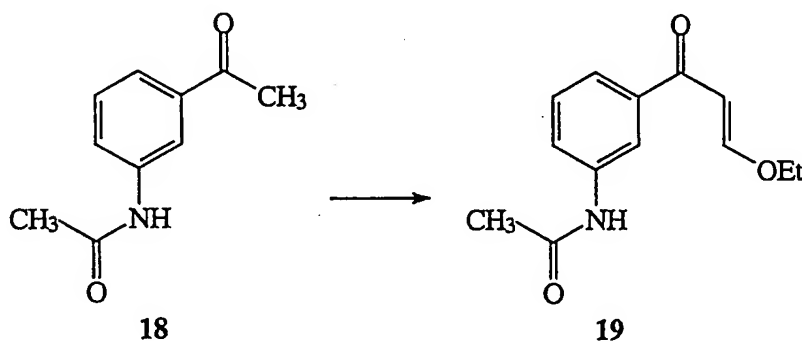
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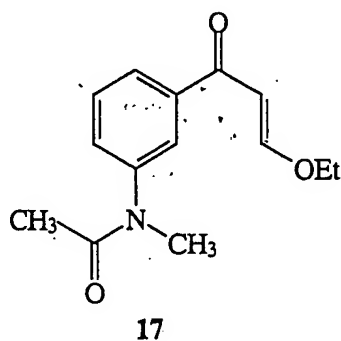
8. A method for making N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1), comprising the following steps:

(a) treating acetophenone 18 with triethyl orthoformate to yield enol ether

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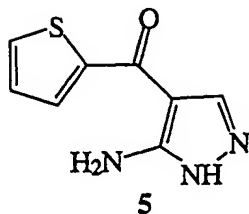
(b) alkylating enol ether 19 to afford enol ether 17



; and

(c) cyclizing enol ether 17 with pyrazole 5 to yield Compound 1





9. The method of any one of claims 1, 2 or 3 wherein enaminone 8 is made by an alkylation step under phase transfer conditions.

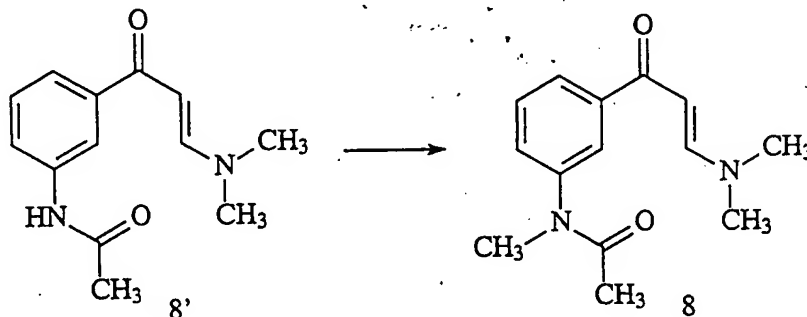
10. The method of claim 9 wherein the phase transfer conditions comprise a phase transfer catalyst in a polar organic solvent with an aqueous phase containing a base.

11. The method of claim 10 wherein the phase transfer catalyst is a quaternary ammonium or phosphonium salt, a crown ether or a polyethylene glycol ether.

12. The method of claim 10 wherein the organic solvent is methylene chloride, benzotrifluoride or toluene.

13. The method of claim 10 wherein the base of the aqueous phase is sodium or potassium hydroxide.

14. A method for making alkylated enaminone 8, comprising the step of alkylating enaminone 8' under phase transfer conditions



15. The method of claim 14 wherein the phase transfer conditions comprise a phase transfer catalyst in a polar organic solvent with an aqueous phase containing a base.

16. The method of claim 15 wherein the phase transfer catalyst is a quaternary ammonium or phosphonium salt, a crown ether or a polyethylene glycol ether.

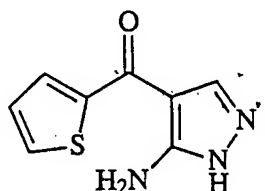
17. The method of claim 15 wherein the organic solvent is methylene chloride, benzonitrile or toluene.

18. The method of claim 15 wherein the base of the aqueous phase is sodium or potassium hydroxide.

19. The method of claim 14, further comprising the step of utilizing enaminone 8 as an intermediate in the synthesis of N-methyl-N-(3-{3-[2-thienylcarbonyl]-pyrazol-[1,5- $\alpha$ ]-pyrimidin-7-yl}phenyl)acetamide (Compound 1).

20. The method of claim 19 wherein the step of utilizing enaminone 8 as an intermediate comprises reacting enaminone 8 with a pyrazole to form Compound 1.

21. The method of claim 20 wherein the pyrazole has the structure:



## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/21924

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D487/04 //(C07D487/04, 239:00, 231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 654 347 A (DUSZA JOHN P ET AL) 31 March 1987 (1987-03-31) cited in the application columns 1, 2, reaction scheme; columns 3, 4, reaction scheme; columns 15, 16, example 52	1, 4, 6-8, 21
A	-& US 4 521 422 A (DUSZA JOHN P ET AL) 4 June 1985 (1985-06-04) cited in the application column 4, reaction scheme; schemes 3, 4, 5; table VII, examples 14, 17, 27, 121, 122, 125, 126, 128	1, 4, 6-8, 21
A	-& US 4 626 538 A (DUSZA JOHN P ET AL) 2 December 1986 (1986-12-02) cited in the application columns 2, 3, reaction schemes	1-3
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

16 November 2000

Date of mailing of the international search report

22/11/2000

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